1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Pouteau et al.
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Filed:	December 29, 2005
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Title:	COMPOSITION FOR TREATING AND/OR PREVENTING DYSFUNCTIONS ASSOCIATED WITH TYPE 2 DIABETES MELLITUS AND INSULIN RESISTANCE
Art Unit:	1614
Examiner:	Unknown
Docket No.:	112701-697

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Applicant is respectfully enclosing the certified copy of the priority document for which priority is claimed for the above-identified application under 35 U.S.C. §119. Specifically, the document enclosed is:

Document No.	Country	Date
03014816.7	**EP**	**June 30, 2003**

The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____
Robert M. Barrett
Reg. No. 30,142
Customer No.: 29157

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TRANSMITTAL FORM

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Firm Name	Bell, Boyd & Lloyd LLP		
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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03014816.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Nestec S.A.
P.O. Box 353
1800 Vevey
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

"Composition for trating and/or preventing dysfunctions associated with Type 2 diabetes mellitus and insulin resistance"

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Composition for treating and/or preventing dysfunctions associated with Type 2 diabetes mellitus and insulin resistance

The present invention relates to the use of a composition comprising acetogenic fibers and at least one compound selected from the group consisting of proteins having a rapid digestion rate, and a mixture of free amino acids, for treating and/or preventing dysfunctions associated with Type 2 diabetes mellitus and/or insulin resistance, and to nutritional or pharmaceutical compositions and functional food products containing these ingredients.

Diabetes mellitus and insulin resistance both are metabolic disorders exhibiting a major common manifestation, hyperglycemia.

Diabetes mellitus originates from an inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency eventually results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves.

There are two principle forms of diabetes, Type 1 and Type 2.

In Type 1 diabetes the pancreas of affected individuals fails to produce insulin largely due to a destruction of the islets of Langerhans, which in most cases seem to occur as a consequence of an auto-immune reaction triggered by some environmental factor, such as a viral infection. Heavy lymphocytic infiltrates appear in and around islets with the number and size of islets being reduced, eventually leading to decreased insulin production and glucose intolerance. This form develops most frequently in children and adolescents, but is being increasingly noted later in life.

Type 2 diabetes results from the body's inability to properly respond to the action of insulin produced by the pancreas. It occurs most frequently in adults, but is being noted increasingly in adolescents as well. The islets of Langerhans are normal in number or somewhat reduced

with type II diabetes mellitus. Fibrosis and deposition of amylin polypeptide within islets are most characteristic of the chronic states of Type 2 diabetes.

Diabetes mellitus of both types is associated with a number of life-threatening and/or handicapping diseases. Examples are nodular and diffuse glomerulosclerosis, which may lead to chronic renal failure. Diabetics are prone to infections, particularly pyelonephritis. Also the eyes may be affected with diabetic retinopathy being one of the leading causes for irreversible blindness. Most persons with Type I diabetes and many of those with Type II diabetes develop some sort of background (non-proliferative) retinopathy. In severe cases, neovascularization may lead to adhesions (synechiae) between iris and cornea or iris and lens, eventually leading to secondary glaucoma with blindness. Also cataracts are more common in diabetics. This predilection for development of cataracts is felt to result from hyperglycemia leading to accumulation of sorbitol that results in osmotic damage to the crystalline lens.

Persons with diabetes mellitus, either Type I or Type II, also exhibit early and accelerated atherosclerosis. The most serious complications of this are atherosclerotic heart disease, cerebrovascular disease, and renal disease, with the most common cause of death being myocardial infarction. Peripheral vascular disease is a particular problem with diabetes mellitus and is made worse through the development of diabetic neuropathy, leading to propensity for injury. Mucormycosis is another feared complication in individuals experiencing diabetes mellitus. The site of involvement is typically the nasopharyngeal region, but the infection can spread to involve soft tissues and bone of the face, orbit, skull, and brain.

The treatment of individuals suffering from diabetes generally involves physical activity, diet and/or administration of medicaments. People with Type 1 diabetes are usually totally dependent on insulin injections for survival, requiring daily administration. Type 2 diabetic patients usually have to observe a strict diet and may additionally receive oral anti-diabetics, such as sulphonyl ureas, alpha-glucosidase inhibitors and biguanides, or even insulin, the intake of which is often associated with severe side effects and complications.

The majority of people suffer from Type 2 diabetes, which accounts for around 90% of all

diabetes cases world-wide. On the molecular level Type 2 diabetes is characterized by a defect of both, insulin secretion and action. The defect of insulin secretion relates mostly to the first phase of the post-prandial insulin release from pancreas, wherein in diabetic patients the already formed insulin is stored within the β-cells, but cannot be released into circulation. Indeed, most of the Type 2 diabetic patients present a resistance to the action of the insulin such that in order to cope with similar glucose concentration as present in healthy people, Type 2 diabetics require a higher concentration of insulin in plasma.

Another type of abnormalities in glucose metabolism is insulin resistance, that is, a reduced sensitivity in the tissues of the body to the action of insulin, which goes along with a perturbed lipid (blood fats) metabolism, obesity, and high blood pressure. This cluster of abnormalities has come to be known as a syndrome, going by a variety of names, including Syndrome X, the Deadly Quartet, and the Insulin Resistance Syndrome.

When insulin resistance, or reduced insulin sensitivity, exists, the body attempts to overcome this resistance by secreting more insulin from the pancreas. The development of Type II, or non-insulin dependent, diabetes occurs when the pancreas fails to sustain this increased insulin secretion. The importance of the Insulin Resistance Syndrome, or perhaps more accurately, "The Pluri-Metabolic Syndrome", lies in its consequences. The syndrome is typically characterized by varying degrees of glucose intolerance, abnormal cholesterol and/or triglyceride levels, high blood pressure, and upper body obesity, all independent risk factors for cardiac disease.

Following a meal, a person suffering insulin resistance will have elevated glucose circulating in the blood, signalling yet more insulin to be released from the pancreas until the glucose is taken up by the cells. Experts suggest that 11 to 25 percent of the adult population may be resistant to insulin to some degree.

Due to the increasing number of affected people world-wide and the changing lifestyle of the society there exists a need in the art to provide additional means useful in preventing, treating and/or improving conditions associated with Type 2 diabetes mellitus and/or insulin

resistance. Moreover, such a means should be essentially free from disadvantageous side-effects well known from many oral anti-diabetics, and should be easy to take up.

This problem has been solved by using a composition comprising acetogenic fibers and/or at least one compound selected from the group consisting of proteins having a rapid digestion rate, and mixtures of free amino acids, for the treatment and/or prevention of dysfunctions associated with Type 2 diabetes mellitus and/or insulin resistance.

During the extensive studies leading to the present invention, it has been found that a composition comprising at least one of these essential ingredients enhances post-prandial insulinemia, decreases blood glucose levels, increases insulin sensitivity, and prevents dyslipidemia, which effects are of course interacting.

The term " acetogenic fiber " as used herein generally refers to a diverse, complex group of substances whose common attribute is their resistance to human digestive enzymes, while giving rise mainly to the formation of acetate in gut, as compared to conventional fibers. "Acetogenic fibers" are defined as dieteray fibers that yield larger amount of acetate in the human large intestine than other conventional dietary fibers. Acetate mainly results from bacterial fermentation of the essentially non-digestible fibers in the gut of humans and non-ruminant animals, respectively. In a preferred embodiment , we may consider that acetatogenic fibers are fibers that yield more than about 600 µmoL of acetate per 100 mg of fibers under 24-h *in vitro* conditions with human inoculums. Examples of such fibers include lactulose, citrus pectin, apple pectin, all pectin, tragacanth, psyllium, pea fiber, inner pea fiber, outer pea fiber, acacia gum, carob bean gum, guar, guar gum, locust bean gum, fructooligosaccharides, inulin, soya fiber and/or citrus pulp, among others.

The term "low-viscous fiber" designates a non-gel forming, low viscosity contributing polymer, made by partial hydrolysis of large polysaccharides and polymers or by polymerization of monomers to a fiber product having a low viscosity in aqueous solutions.

The term "protein having a rapid digestion rate" is meant to designate any proteinaceous material which may be rapidly broken down in the gastro-intestinal tract of the individual and absorbed, i.e. either it is digested rapidly in its native form or has been modified to accelerate its digestion rate. Rapidly digested proteins induce a dramatic but short increase in plasma amino acids, on the opposite to slowly digested proteins, which induce a mild but prolonged plateau of hyperaminoacidemia (Boirie et al, Proc. Natl. Acad. Sci. USA, 1997, 94:14930-5). Examples of such proteins are polypeptides in their native form or enzymatic partial degradation products, or treated with a transglutaminase, or mixed with anionic polysaccharides.

The term "mixture of free amino acids" is meant to designate a mixture comprising at least two, preferably at least four different amino acids, selected from the known natural occurring amino acids.

A large variety of well-known acetogenic fibers may be used in a composition according to the present invention, such as e.g. lactulose. In particular, preferred are low-viscous fibers. The acetogenic fiber may be incorporated in the present composition in an amount of from about 0.2 to 90 % by weight, preferably from 0.5 to 70 % by weight, more preferably 0.7 to 30 % by weight, even more preferably 5 to 25 % by weight, most preferred about 7% by weight, based on the total weight of the composition.

It has been noted that an addition of acetogenic fibers to a nutritional composition provides advantages exceeding the well-known advantages of a fiber addition to a nutritional composition.

It has been known that a supplementation of food with dietary fibers may be helpful in preventing or treating a large variety of disorders, such as constipation, intestinal toxemia, cholelithiasis, colon cancer, and colitis, etc. and may positively influence lipid metabolism by interfering with cholesterol absorption, changing lipoprotein lipase activity or fatty acid metabolism. Some of the positive effects generally associated with a fiber supplementation of food have been associated with the formation of short chain fatty acids (SCFAs: acetate,

propionate and butyrate) as products of bacterial fermentation of fibers in the gut. Among these SCFAs, acetate is the major product and is known to be readily absorbed by the colonic mucosa, and it has been shown that acetate supplies 6 to 10 % of the basal energy expenditure in non-ruminants. In particular, acetate may be activated into acetyl-CoA and later involved in free fatty acid synthesis for the building of epithelial membranes or may enter mitochondria yielding ketone bodies and providing energy.

Surprisingly, the present inventors have now found that acetogenic fibers have significant effects in improving insulin sensitivity, and in particular, in re-establishing normal insulin-sensitivity and thus a normal systemic metabolism. The positive effects of an administration of acetogenic fibers become even more pronounced when administered in a composition according to the present invention comprising at least one of the other ingredients illustrated.

Without wishing to be bound to any theory it is presently assumed that an increased amount of acetate in blood and tissues - resulting from an administration of a composition according to the present invention - implies a reduced lipolysis, i.e. a reduced liberation of glycerol and fatty acids from tissues into the blood. This could result in a comparatively lower amount of free fatty acids, which may be bound to insulin receptors, which in turn could imply the surprising effect that the insulin receptors recover a sensitivity as present in healthy persons or at least an improved insulin sensitivity.

The proteinaceous material to be used in the present composition has to exhibit a rapid digestion rate. Examples for such proteins having a rapid digestion rate are acid or sweet whey protein, soy protein, pea protein, and the like. Also degradation products of such or other proteins may be utilized, which may be obtained e.g. by subjecting the proteins to a peptidase/protease for a time sufficient to yield a particular degradation of the starting product. The proteins having a rapid digestion rate may be present in the composition in an amount of from about 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 60 % by weight, even more preferably 21 to 40 % by weight and most preferably about 25 to 35 % by weight, on the basis of the total dry weight of the composition.

It has been found that the present kind of proteinaceous materials has a particular performance after consumption by type 2 diabetes patients. According to the studies carried out proteins having a rapid digestion rate significantly increase the production and/or secretion of insulin, as determined by an increase in the maximal plasma concentration and bio-availability of pro-insulin, insulin and C-peptide. The C-peptide results from the formation of biological active insulin from pro-insulin and serves as an indicator showing how much insulin is produced in an individual. C-peptide is considered to represent the most accurate indicator for the production of insulin in ß-cells.

In view of this the present inventors concluded that proteins having a rapid digestion rate are enhancing post-prandial insulinemia, and restore, at least partially, the first phase of the insulin response of diabetic patients to a standard meal. According to the present invention, the kinetics of post-prandial insulinemia provoked by dietary carbohydrates may be accurately modulated by protein supplements with specific digestion rates.

In addition thereto, during the studies relating to the effects of proteins having a rapid digestion rate the present inventors unexpectedly also noted that a mixture of free amino acids has a positive influence on the glucose level in the blood of individuals as well, and this even more pronounced.

As amino acids to be used in the present composition any of the known natural amino acids or also modified amino acids may be utilized. Preferably, the mixture of free amino acids will resemble an amino acid profile as found in dietary proteins, preferably dairy proteins, e.g. whey, egg or casein protein, fish or meat proteins. If desired, the content of one or more amino acids may be enriched, such as e.g. leucine, phenylalanine or tyrosine. The free amino acids may also be added in form of extensive protein hydrolysates from which the free amino acid content has been determined.

A composition for use in the present invention may comprise of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 60 % by weight, even more

preferably 21 to 40 and most preferred of from about 25 to 35 % by weight of an amino acid mixture, on the basis of the total dry weight of the composition.

It could be shown that providing a mixture of free amino acids ensues an increased bioavailability and an increased maximal plasma concentration of pro-insulin and insulin in the type 2 diabetes patient. Moreover, a free amino acid composition, when ingested together with a standard diet results in a significant decrease in the plasma concentration of glucose.

The composition with the ingredients as detailed above may therefore advantageously be used for treating, preventing and/or improving metabolic dysfunctions and/or conditions associated with Type 2 diabetes mellitus or insulin resistance, via e.g. enhancing post-prandial insulinemia, decreasing blood glucose levels, increasing insulin sensitivity, or preventing dyslipidemia.

The present composition will also be of high interest for large parts of the population, which are not suffering from insulin resistance or Type 2 diabetes mellitus at present, but belong to a target group at risk to develop any of said disorders, either due to a high risk diet or genetic predisposition. Moreover, an enhancement of post-prandial insulinemia and/or an increase in insulin sensitivity is also highly interesting for other groups of persons, such as patients recovering from diseases or trauma leading to muscle depletion, exercising persons or elderly persons, since insulin is an anabolic hormone necessary for muscle mass maintenance and growth. High post-prandial insulinemia therefore promotes improving muscle mass accretion in exercising persons, is helpful for patients suffering from muscle depletion, and supports muscle maintenance in elderly persons. Depending on the target group to whom the composition will be administered, either needing a more pronounced improvement of insulin sensitivity, or a more intensive enhancement of post-prandial insulinemia, and/or a more intensive decrease of blood glucose levels, etc., the amounts of acetogenic fibers, proteins having a rapid digestion rate and mixtures of free amino acids may be appropriately selected.

The composition as described above may of course also be used for the manufacture of a so called functional food product or a pharmaceutical composition.

According to another aspect, the present invention also pertains to a nutritional or pharmaceutical composition comprising acetogenic fibers, and at least one of the components selected from the group consisting of proteins having a rapid digestion rate and free amino acid mixtures, each in the amounts indicated above.

During the first administrations of the composition according to the invention, one have to keep in mind that fibers have to be digested in the colon; therefore, it is preferable that the composition is absorbed between 3 and 7 hours before a meal, for example 4 hours. After a few administrations of the composition according to the invention, we observe an increased insulin sensitivity, and in that second phase the present composition may be consumed either together with a meal, in particular a meal containing carbohydrates, or shortly before or after such a meal, such as up to half an hour, or preferably, up to 10 minutes before or after such a meal. The composition may be taken separately or as a supplement to a meal.

During the first phase, when fibres have to be ingested a few hours before a meal, it is possible, if not desirable, to provide two compositions to the patient in order to obtain the best effect. The first composition, comprising acetogenic fibres, should be ingested between 3 and 7 hours before a meal, for example 4 hours. The second composition, comprising proteins having a rapid digestion rate and /or a mixture of free amino acids, should be ingested shortly before or after a meal.

Particularly good results may be achieved when providing at least 0.1 g of acetogenic fibers per kg body weight, more preferably between 0.1 to 2 g of acetogenic fibers per kg body weight, most preferably between 0.3 to 0.8 g of acetogenic fibers per kg body weight, even more preferably 0.5 g of acetogenic fibers per kg body weight in combination or not with at least 0.1 g of a mixture of free amino acids and/or at least 0.1 g proteins having a rapid digestion rate per kg body weight, more preferably in combination with 0.1 to 1 g of a mixture of free amino acids and/or 0.1 to 1 g proteins having a rapid digestion rate per kg body weight, most preferably in combination with 0.5 to 0.8 g of a mixture of free amino acids and/or 0.5 to 0.8 g proteins having a rapid digestion rate per kg body weight, e.g.

during, before or after a standard meal, in particular a standard meal comprising carbohydrates. A standard meal is any meal comprising at least 150 kcal, more preferably at least 250 kcal.

The nutritional composition according to the present invention is preferably enterally administrable, such as in form of a powder, a liquid concentrate, or a ready-to-drink beverage. The composition can be directly consumed or admixed with various foodstuffs, in particular to ready-to-use snacks, dairy products or drinks, or used for the preparation of an oral or enteral nutritional composition or a fruit juice.

Depending on the desired application, i.e. whether e.g. mainly an improvement of insulin sensitivity and/or an enhancement of post-prandial insulinemia and/or a decrease of blood glucose levels, etc. is aimed at, the weight ratios of acetogenic fibers ("x"), proteins having a rapid digestion rate ("y") and free amino acids ("z") may vary e.g. between within the proportion x : y : z, wherein x and one of y and z are each selected between 0.1 and 10, preferably 0.5 and 5, more preferably 0.5 and 2, and the other one of y and z is selected between 0 and 10, preferably 0.1 and 5, more preferably 0.5 and 2.

In particular, the weight ratio of acetogenic fibers versus the combination of proteins having a rapid digestion rate and free amino acids may vary e.g. between (0.1 to 10) : (0.1 to 20), preferably (0,5 to 5) : (0,5 to 8), more preferably (0.5 to 1) : (1 to 2). The weight ratio of proteins having a rapid digestion rate versus free amino acids may vary e.g. between (1 to 10) : (1 to 10), preferably between (1 to 5) : (1 to 5) and more preferably between (2 to 4) : (2 to 4).

A composition according to the present invention may of course comprise other conventional ingredients, such as vitamins and minerals, fibers, fat, food additives etc..

In particular, vitamins and minerals may be present in an amount of between 30 % and 150 % of US RDA (US recommended (daily) dietary allowance) per daily dosage. Additionally, one or more food grade emulsifiers may be included in the nutritional

composition, if desired, such as diacetyl tartaric acid esters of mono- and diglycerides, lecithin, and mono- or diglycerides or a mixture thereof. Similarly, suitable food-acceptable salts and/or stabilizers may also be included.

If desired in addition to acetogenic fibers also other fibers, both soluble and insoluble fibers may be included.

Depending on the desired application, a nutritional formula may include a fat source, preferably comprising about 5% to 40 % of the energy (measured in calories) on the basis of the total energy of the nutritional composition; preferably, about 10 % to about 20 % of the energy. Lipid making up the fat source may be any suitable fat or fat mixture. Vegetable fat is particularly suitable, for example soy oil, palm oil, coconut oil, safflower oil, sunflower oil, corn oil, canola oil, lecithin and the like. Animal fat such as milk fat may also be added if desired.

According to one aspect of the present invention, the preparation of nutritional compositions is intended which are essentially free or comprise less than 10 % by weight, preferably less than 5 % by weight, more preferably less than 1 % by weight of an additional carbohydrate source. For some applications, such as e.g. ready-to-use beverages, nutritional formulas are advantageous which are essentially free or comprise less than 5 % by weight of mono-saccharides, or wherein the mono-saccharides comprise less than 40 % by weight, preferably less than 10 % by weight, more preferably less than 1 % by weight of glucose, galactose or tagatose, each on basis of the total weight of mono-saccharides, or are essentially free of glucose, galactose or tagatose.

For some formulas, such as ready-to-use snacks, however, also an addition of a carbohydrate source may be advantageous, preferably in an amount to provide 1 to 70 %, more preferably 25 % to 45 % of the energy on basis of the total energy of the nutritional composition.

Preparations comprising a composition according to the present invention may also include non-caloric sweeteners, flavorings and food-acceptable colorings.

A particularly advantageous embodiment comprises a fluid nutritional or pharmaceutical preparation, such as a ready-to-use beverage, on basis of fruit juice, vegetable juice, water, isotonic drinks, carbonated flavored drinks, soft drinks, teas, coffees, dairy products, meat and/or vegetable soups or mixtures thereof, which may be supplemented with minerals, vitamins and/or carbonic acid, if desired. Beverages comprising fruit or vegetable juices provide additionally the advantage of comprising vitamins, minerals or even enzymes and provide an advantageous complementation of a nutritional composition according to the present invention. In particular, juices such as orange, apple, pineapple, grapefruit, lemon, lime, mango, passion fruit, elderberries, cranberries, currants, grape, tomato, carrot or combinations thereof may form the basis for a ready-to-use beverage.

A fluid nutritional or pharmaceutical preparation may comprise from 11 to 97 % by weight, preferably from 21 to 80 % by weight, most preferably from 61 to 75 % by weight, of any of the before-mentioned juices, beverages, water or mixtures thereof, and from 3 to 89 % by weight, preferably from 20 to 79 % by weight, most preferably from 25 to 39 % by weight, of a composition according to the present invention, on basis of the total weight of the fluid preparation. When preparing a fluid preparation preferably a composition will be used, comprising the acetogenic fibers, and in addition thereto 1 to 20 % by weight proteins having a rapid digestion rate, and/or 1 to 20 % by weight free amino acids, more preferably a composition will be used, comprising the acetogenic fibers, and in addition thereto, 5 to 12 % by weight proteins having a rapid digestion rate and/or 5 to 12 % by weight free amino acids.

Advantageously, a beverage according to the present invention delivers 1 to 150 kcal, preferably 21 to 100 kcal, more preferably 31 to 50 kcal per 100 g of fluid preparation. For example, a beverage accompanying a standard meal may e.g. provide per dosage (i.e. per standard meal) 0.1 to 100 g, preferably 5 to 40 g acetogenic fibers, more preferably 10 to 30 g acetogenic fibers, even more preferably 20 g acetogenic fibers. If associated with proteins having a rapid digestion rate and/or amino acid mixtures, the ranges are preferably 40 to 60 g of one selected from protein having a rapid digestion rate and amino acid mixture, and 1 to

100 g, preferably 15 to 50 g of the other one selected from protein having a rapid digestion rate and amino acid mixture.

Of course, such a beverage may also be obtained by admixing a composition according to the present invention to a beverage (e.g. according to instructions on the package), which admixing may be performed e.g. by the consumers themselves before consumption.

Alternatively, a food product may be enriched with a composition according to the present invention. For example, a fermented milk, a yoghurt, a fresh cheese, a renneted milk, a confectionery bar, breakfast cereal flakes or bars, a drink, milk powder, soy-based product, non-milk fermented product or a nutritional supplement for clinical nutrition. Then, the amount of the composition added is preferably, at least 0.5 % by weight, more preferably 11 to 40 % by weight, on basis of the total weight of the food product.

Food products or beverages as detailed above, provide the advantage that they may be consumed shortly before, during, or shortly after a meal by a person, in particular from a person suffering from Type 2 diabetes, and permit an easy solution for enhancing post-prandial insulinemia, restoring, at least partially, the first phase of the insulin response to a standard meal, decreasing blood glucose levels, increasing insulin sensitivity, and preventing dyslipidemia. Thus, compositions according to the present invention may be helpful in significantly increasing the quality of life of large groups of the population.

A composition according to the present invention may also be used for the preparation of an enteral nutritional formula, in particular for patients suffering from muscle depletion or for supporting muscle maintenance.

Compositions according to the present invention may be designed both for human consumption and for consumption by a companion animal, in particular for dogs and cats.

All before-mentioned products according to the present invention provide the advantage that they may be expected to be highly accepted by the consumers as they are formulated on basis

of well-known nutritional components, which proved to be essentially free of undesired side-effects. Moreover, compositions according to the present invention are essentially free of unpleasant tastes and may be regularly, e.g. daily consumed.

According to another aspect, the invention also provides a method for treating or preventing metabolic dysfunctions and/or improving conditions associated with Type 2 diabetes mellitus or insulin resistance which comprises administering an effective amount of a composition according to the present invention.

The following examples are given by way of illustration only and should not be construed as limiting the subject-matter of the present application.

Example 1

Influence of protein on the insulin response

This example demonstrates the effect of the protein digestion rate and compares the effect of an administration of protein versus a corresponding mixture of free amino acids on the post-prandial activation of the entero-insular axis, as assessed by the postprandial kinetics of plasma C-peptide (C_{max}, T_{max} and AUC) in Type 2 diabetic patients.

The following abbreviations are used:

C_{max} is the maximal plasma concentration of a compound, T_{max} is time to achieve C_{max}, AUC is the area under the plasma concentration curve versus time, and p is the treatment effect.

Second, this example shows the effect of the protein digestion rate and compares the effect of an administration of protein versus a corresponding mixture of free amino acids (assessed as kinetics of amino acid appearance in plasma) on the postprandial plasma levels of the hormones and metabolites: GLP-1, insulin, proinsulin, glucagon, glucose, triglycerides and cholesterol in Type 2 diabetic patients.

The following three regimens were administered:

- Treatment with sweet whey protein isolate (Lacprodan DI-9224, Arla Foods, Denmark), a protein which is providing for a rapid digestion rate (labelled with code "S1" below);
- Treatment with micellar casein (Promilk 852B, Ingredia Lactoprosperité AG, Switzerland), a comparative protein providing an essentially slow protein digestion rate (labelled with code "S2" below);
- Treatment with a mixture of free L-amino acids resembling to the casein composition (Individual amino acids were obtained from Ajinomoto Europe Sales GMBH, Germany) labelled with code "S3" below);.

Each regimen was a protein powder and was reconstituted in a liquid form by mixing 100 g of protein powder with 900 g water. This solution delivers 40 kcal and 10 g protein per 100 g. Formula dosage depends on patient weight: 7 g liquid formula/kg body weight (BW) (0.7 g protein/kg BW). It was administrated as part of a test meal (6 kcal/kg BW; 38% carbohydrates, 15% lipids and 47% proteins). In order to obtain a high insulin response allowing for product discrimination, the protein solutions were ingested with carbohydrates and lipids (bread and chocolate spread) and the amount of protein was relatively high (around 2/3 of the protein daily requirements).

Study setup

The study was designed as a double-blind, single center, exploratory, randomized and controlled cross-over clinical trial. It has been carried out at the Centro Antidiabetico, Azienda Ospedaliera de Padova, Italy. The subjects were Type 2 diabetic patients. The treatments were blind to patients and to the study staff. Patients received once each treatment with a wash-out period of at least 2 weeks between treatments.

The study was performed on Type 2 diabetic patients of both sexes aged between 31 to 65 years from the outpatient diabetic subjects scheduled to be regularly visited at the Centro Antidiabetico of the Azienda Ospedialera of Padova.

The inclusion criteria were: more than 3 years of disease; defective endogenous insulin secretion [C-peptide response peak after iv glucagon ≤ 3 mg/ml]; age: 30 - 65 years; 18 < BMI (Body Mass Index) < 30 kg / m^2; having obtained his/her informed consent; diet and/or OHA (oral hypoglycaemic agent)-treated.

The exclusion criteria were: treated with insulin; patients with moderate to severe kidney or liver insufficiency, respiratory or cardiac failure, endocrinopathies other than diabetes, and major diseases of the GI tract causing malabsorption; patients who cannot be expected to comply with the treatment; currently participating or having participated in another clinical trial during the last 3 months prior to the beginning of this study.

Each subject consumed all three test treatments once in random order. The test period lasted one day. Twenty-four hours before and during test day, the patients had to interrupt the OHA therapy. At test day, the patients came to the hospital after overnight fasting. After placing an indwelling catheter in the patient arm, and taking two basal blood samples, patients consumed the test meal. The test meal included a liquid formula containing one of the three treatments. Blood sampling was done at -10, 0, 10, 20, 30, 60, 90, 120, 150 and 180 minutes of the test meal intake.

Data collection, management and validation

The following data were collected:

Test periods

- Blood parameters: for each test period, the blood was collected for 190 minutes (2 samples before and 8 samples after the test meal). Then, the following plasmatic parameters were measured:
  - *amino acids:* taurine, aspartate, threonine, serine, asparagine, glutamate, glutamine, proline, glycine, alanine, citrulline, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan, ornithine, lysine, histidine and arginine.
  - *hormones and metabolites:* proinsulin, insulin, GLP-1, GIP, glucagon, glucose, C-

peptide, triglycerides and total cholesterol.

- Anthropometric measures: weight and height immediately before the test meal.

Statistical methods

Statistical analyses planned in the protocol

The primary and secondary outcomes were analyzed by using a linear mixed-effect model with the three treatments and sex as fixed effects and subject as random effect. The results include: mean ± standard deviation and 95% confidence interval for mean difference. The rejection level in statistical tests was equal to 5% (p=0.05). For the pairwise comparison between two treatments, the rejection level was set to 2% (p=0.02, Bonferroni correction). The statistical analyses were done using SAS software (version 8.2).

Calculations of the kinetic parameters

AUC is the area under the plasma concentration curve versus time. It is calculated by the trapezoidal rule as follows:

$$AUC = \frac{1}{2}\sum_{i=1}^{n-1} (T_{i+1} - T_i)\,(C_{i+1} + C_i - 2B)$$

where T_i is the i^{th} time value, C_i is the i^{th} concentration value, n is the number of time values and B is the baseline value. The kinetic parameters were calculated using NCSS2000 software.

Results

Compliance

For each test meal, the average amounts of bread, chocolate spread and protein drink are 27.46 ± 3.97 g of bread, 20.85 ± 3.00 g of chocolate and 487 ± 70 g of protein drink.

Primary outcome: Plasmatic C-peptide

The kinetic parameters of C-peptide [$AUC_{(0\text{-}180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Tables 2.

*Table 1-a: $AUC_{(0-180min)}$ of C-peptide [(ng/ml)*min]*

DESCRIPTIVE STATISTICS	TREATMENT		
	"Whey protein" S1	"Casein" S2	"Free amino acids" S3
N	12	11	12
Mean	672	572	654
± SD	268	213	269
95% CI	[502; 843]	[428; 715]	[483; 825]
Minimum	385	291	394
Median	570	552	560
Maximum	1213	901	1215
[S1 – S2]	122 ± 82 (SE= 35) [50; 193]		
[S3 – S2]	104 ± 82 (SE= 35) [32; 176]		
[S1 – S3]	18 ± 82 (SE= 33) [-52; 87]		

Mean ± standard deviation; [ ]; 95% confidence interval for mean; SE; Standard error of the mean; SD (standard deviation); CI (confidence interval).

The bioavailability [$AUC_{(0-180min)}$] is significantly different between the treatments (p= 0.004). The AUC of treatment [S2; "casein"] is significantly lower than [S1; "whey protein"] (p= 0.002) and [S3; "free amino acids"] (p= 0.007).

Table 1-b: C_{max} of C-peptide [ng/ml]

DESCRIPTIVE STATISTICS	TREATMENT		
	"Whey protein" S1	"Casein" S2	"Free amino acids" S3
N	12	11	12
Mean	5.11	4.33	4.87
± SD	2.23	1.47	1.94
95% CI	[3.70; 6.52]	[3.34; 5.32]	[3.63; 6.10]
Minimum	2.76	1.88	2.68
Median	4.90	4.36	4.43
Maximum	10.40	6.20	9.00
[S1 – S2]	0.94 ± 0.84 (SE= 0.35) [0.21; 1.67]		
[S3 – S2]	0.70 ± 0.84 (SE= 0.35) [-0.03; 1.42]		
[S1 – S3]	0.24 ± 0.84 (SE= 0.34) [-0.47; 0.95]		

Mean ± standard deviation; [ ]: 95% confidence interval for mean; SE: Standard error of the mean; SD (standard deviation); CI (confidence interval).

C_{max}, i.e. the maximal plasma concentration of the C-peptide, is significantly different between the treatments (p= 0.040). The C_{max} of treatment [S2; "casein"] is significantly lower

than [S1; "whey protein"] (p= 0.015).

Table 1-c: T_{max} to reach the C_{max} of C-peptide [min.]

DESCRIPTIVE STATISTICS	TREATMENT		
	"Whey protein"	"Casein" S2	"Free amino acids"
N	12	11	12
Mean	117	129	135
± SD	24	54	39
95% CI	[102; 132]	[93; 165]	[111; 160]
Minimum	80	15	80
Median	127	138	130
Maximum	145	206	204
[S1 – S2]	-10 ± 34 (SE= 14) [-40; 19]		
[S3 – S2]	8 ± 34 (SE= 14) [-22; 37]		
[S1 – S3]	-18 ± 34 (SE= 13) [-47; 10]		

Mean ± standard deviation; [ ]: 95% confidence interval for mean; SE: Standard error of the mean ; SD (standard deviation); CI (confidence interval).

T_{max}, i.e. the time to reach the maximal plasma concentration of the C-peptide C_{max} is not significantly different between the three treatments (p= 0.43).

Secondary outcomes : Hormones and metabolites

Proinsulin

Proinsulin is a precursor of insulin, which is obtained after cleavage of the C-peptide and after formation of S-S-bridges. The kinetic parameters of proinsulin ($AUC_{(0\text{-}180min)}$, C_{max} and T_{max}) for the three treatments are summarized in Table 2.

Table 2: Kinetic parameters of proinsulin

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(pM) * min]	752 ± 1189 [-329; 1834]	-1429 ± 1189 [-2546; -312]	-677 ± 1189 [-1707; 354]	p = 0.047
C_{max} (pM)	8 ± 7 [1; 15]	-10 ± 7 [-17; -3]	-2 ± 7 [-9; 4]	p = 0.014
T_{max} (min)	-26 ± 26 [-49; -3]	8 ± 26 [-15; 31]	-18 ± 26 [-39; 4]	p = 0.073

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 1 to 180 minutes, the plasmatic amount of proinsulin (bioavailability) with the treatment [S2; "casein"] is significantly lower than with [S3; "free amino acids"] ($p= 0.01$). C_{max} of proinsulin with the treatment [S2; "casein"] is significantly lower than with the treatment [S3; "free amino acids"] ($p< 0.005$). T_{max} of proinsulin is not significantly different between the three treatments ($p= 0.07$).

Insulin

The kinetic parameters of insulin ($AUC_{(0-180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 3.

Table 3: Kinetic parameters of insulin

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(μU/ml) * min]	1052 ± 1139 [56; 2049]	-1339 ± 1139 [-2336; -343]	-287 ± 1139 [-1254; 680]	p = 0.047
C_{max} (μU/ml)	13 ± 12 [3; 24]	-14 ± 12 [-24; -4]	-1± 12 [-11; 9]	p = 0.016
T_{max} (min)	-7 ± 37 [-40; 25]	-0.07 ± 37 [-32; 32]	-7 ± 37 [-39; 24]	p = 0.86

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 180 minutes, the plasmatic amount of insulin (bioavailability) with the treatment [S2; "casein"] is significantly lower than with [S3; "free amino acids"] ($p= 0.01$). C_{max} of insulin with the treatment [S2; "casein"] is significantly lower than with the treatments [S1; "whey protein"] ($p= 0.014$) and [S3; "free amino acids"] ($p= 0.009$). T_{max} of insulin is not significantly different between the three treatments ($p= 0.86$).

Glucagon

Glucagon is a polypeptide hormone formed in the pancreas. The kinetic parameters of glucagon ($AUC_{(0-180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 4.

Table 4: Kinetic parameters of glucagon

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(µg/L) * min]	3955 ± 6311 [-1473; 9382]	-5349 ± 6311 [-10777; 78]	-1395 ± 6311 [-6650; 3860]	p = 0.13
C_{max} (µg/L)	78 ± 84 [4; 152]	-62 ± 84 [-136; 12]	16± 84 [-56; 88]	p = 0.10
T_{max} (min)	15 ± 24 [-5; 36]	-4 ± 24 [-24; 17]	12 ± 24 [-8; 32]	p = 0,29

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 180 minutes, the plasmatic amount of glucagon (bioavailability) with the treatments [S1], [S2] and [S3] is not significantly different (p= 0.13). C_{max} of glucagon with the treatments [S1], [S2] and [S3] is not significantly different (p= 0.10). T_{max} of glucagon is not significantly different between the three treatments (p= 0.29).

As becomes obvious from the results above, none of said three treatments has a significant influence with respect to glucagon, a hormone which could give rise to an undesired blood sugar increase.

Glucose

The kinetic parameters of glucose ($AUC_{(0\text{-}180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 5.

Table 5: Kinetic parameters of glucose

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(mg/dl) * min]	-1447 ± 3533 [-4487; 1592]	3859 ± 3533 [743; 7009]	2412 ± 3533 [-529; 5354]	p = 0.044
C_{max} (mg/dl)	-7 ± 18 [-23; 9]	27 ± 18 [11; 43]	20± 18 [4; 35]	p = 0.006
T_{max} (min)	1 ± 31 [-26; 29]	-11 ± 31 [-38; 16]	-10 ± 31 [-36; 17]	p = 0.66

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 180 minutes, the plasmatic amount of glucose (bioavailability) with the treatment [S3; "free amino acids"] is significantly lower than with the treatment [S2; "casein"] (p= 0.015). C_{max} of glucose with the treatment [S3; "free amino acids"] is significantly lower than with the treatment [S2; "casein"] (p= 0.002). T_{max} of glucose is not significantly different between the three treatments (p= 0.66).

GIP (Gastric Inhibitory Peptide)

GIP (Gastric Inhibitory Peptide) is a gastrointestinal hormon which inhibits the liberation of insulin. The kinetic parameters of GIP ($AUC_{(0-150min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 6.

Table 6: Kinetic parameters of GIP

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(pM) * min]	343 ± 1260 [-442; 1128]	1178 ± 1260 [368; 1988]	1521 ± 1260 [736; 2306]	p = 0.002
C_{max} (pM)	0 ± 15 [-10; 9]	10 ± 15 [0; 19]	9 ± 15 [0; 19]	p = 0.09
T_{max} (min)	-10 ± 52 [-42; 22]	-5 ± 52 [-38; 27]	-15 ± 52 [-47; 17]	p = 0.61

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 150 minutes, the plasmatic amount of GIP (bioavailability) with the treatment [S3; "free amino acids"] is significantly lower than with the treatments [S1; "whey protein"] (p< 0.001) and [S2; "casein"] (p= 0.007). C_{max} of GIP is not significantly different between the three treatments (p= 0.09). T_{max} of GIP is not significantly different between the three treatments (p= 0.61).

Total cholesterol

The kinetic parameters of total cholesterol ($AUC_{(0-180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 7.

Table 7: Kinetic parameters of total cholesterol

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(mg/dl) * min]	-1273 ± 3318 [-4127; 1581]	211 ± 3318 [-2643; 3065]	-1062 ± 3318 [-3825; 1701]	p = 0.62
C_{max} (mg/dl)	-6.70 ± 18 [-22; 9]	-0.28 ± 18 [-15; 6]	-6 ± 18 [-21; 9]	p = 0.59
T_{max} (min)	11 ± 42 [-26; 47]	16 ± 42 [-21; 52]	26 ± 42 [-10; 62]	p = 0.30

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 180 minutes, the plasmatic amount of total cholesterol (bioavailability) is not significantly different between the treatments [S1], [S2] and [S3] (p= 0.62). C_{max} of cholesterol is not significantly different between the treatments [S1], [S2] and [S3] (p= 0.59). T_{max} of cholesterol is not significantly different between the three treatments (p= 0.33).

This example shows that an administration of a mixture of free amino acids or of a protein having a rapid digestion rate is not associated with a negative effect with respect to the cholesterol level in blood.

Triglycerides

The kinetic parameters of triglycerides ($AUC_{(0-180min)}$, C_{max} and T_{max}) from the three treatments are summarized in Table 8.

Table 8: Kinetic parameters of triglycerides

KINETIC PARAMETERS	DIFFERENCE BETWEEN THE TREATMENTS			TREATMENT EFFECT
	[S1 – S2]	[S2 – S3]	[S1 – S3]	
AUC [(mg/dl) * min]	-454 ± 3727 [-3660; 2753]	183 ± 3727 [-3024; 3388]	-271 ± 3727 [-3375; 2833]	p = 0.96
C_{max} (mg/dl)	-13 ± 27 [-37; 11]	16 ± 27 [-8; 39]	2 ± 27 [-20; 25]	p = 0.36
T_{max} (min)	-19 ± 53 [-65; 27]	13 ± 53 [-33; 59]	-6 ± 53 [-51; 39]	p = 0.69

Mean ± standard deviation; [ ] : 95% confidence interval for mean difference.

Between 0 and 180 minutes, the plasmatic amount of triglycerides (bioavailability) is not significantly different between the treatments [S1], [S2] and [S3] (p= 0.96). C_{max} of triglycerides is not significantly different with the treatments [S1], [S2] and [S3] (p= 0.36). T_{max} of triglycerides is not significantly different between the three treatments (p= 0.69).

This example shows that an administration of a mixture of free amino acids or of a protein having a rapid digestion rate is not associated with a negative effect with respect to the trigyceride level in blood.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications will be covered by the appended claims.

Claims

1. Use of a composition comprising acetogenic fibers, and/or at least one compound selected from the group consisting of proteins having a rapid digestion rate and mixtures of free amino acids, for the preparation of a nutritional and/or a pharmaceutical composition for treating, preventing and/or improving metabolic dysfunctions and conditions associated with Type 2 diabetes mellitus or insulin resistance.

2. The use of a composition according to claim 1, wherein said acetogenic fiber is lactulose, citrus pectin, apple pectin, all pectin, tragacanth, psyllium, carob bean gum, guar, guar gum, locust bean gum, fructooligosaccharides, pea, inner pea, acacia gum, inulin, soya and/or citrus pulp.

3. The use according to claim 2, wherein the amount of acetogenic fibers in the composition is in the range of from 0.2 to 90 % by weight, preferably from 0.5 to 50 % by weight, more preferably 0.7 to 30 % by weight, even more preferably 5 to 25 % by weight, most preferred about 7 % by weight, based on the total weight of the composition.

4. The use of a composition according to any of the preceding claims, wherein said proteins having a rapid digestion rate are selected from the group consisting of acid or sweet whey protein, soy protein, pea protein.

5. The use according to claim 4, wherein the amount of proteins in the composition is in the range of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

6. The use of a composition according to any of the preceding claims, wherein the amount of the mixture of amino acids in the composition is in the range of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

7. The use of a composition according to any of the preceding claims, for enhancing post-prandial insulinemia, stimulating insulin production, increasing insulin sensitivity, preventing dyslipidemia and/or decreasing blood glucose levels.

8. The use of a composition according to any of the preceding claims, in the manufacture of a functional food.

9. Nutritional or pharmaceutical composition comprising acetogenic fibers, and at least one of the components selected from the group consisting of proteins having a rapid digestion rate and a mixture of free amino acid, each in an amount in the range of from about 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

10. The composition according to claim 9, wherein said acetogenic fiber is lactulose, citrus pectin, apple pectin, all pectin, tragacanth, psyllium, carob bean gum, guar, guar gum, locust bean gum, fructooligosaccharides, pea, inner pea, acacia gum, inulin, soya and/or citrus pulp.

11. The composition according to claim 9 or 10, wherein the proteins are selected from the group consisting of acid or sweet whey protein, soy protein, pea protein.

12. The composition according to any of the claims 9 to 11, comprising 11 to 97 % by weight of a fluid selected from the group consisting of fruit juice, vegetable juice,

water, isotonic drinks, carbonated flavored drinks, soft drinks, teas, coffees, dairy products, meat and/or vegetable soups or mixtures thereof, and 3 to 89 % by weight of a composition according to claim 9 to 11, all on the basis of the total weight of the fluid preparation

13. The composition according to one of claims 9 to 1, wherein said nutritional or pharmaceutical composition is a fermented milk, a yoghurt, a fresh cheese, a renneted milk, a confectionery bar, breakfast cereal flakes or bars, a drink, milk powder, soy-based product, non-milk fermented product or a nutritional supplement for clinical nutrition.

14. A method for treating, preventing and/or improving metabolic dysfunctions or conditions with Type 2 diabetes mellitus or insulin resistance which comprises administering an effective amount of a composition according to claim 7 to 10.

Abstract

The present invention relates to the use of a composition for treating, preventing and/or improving metabolic dysfunctions associated with Type 2 diabetes mellitus and insulin resistance, said composition comprising acetogenic fibers, and/or at least one compound selected from the group consisting of proteins having a rapid digestion rate, and mixtures of free amino acids, and to nutritional or pharmaceutical compositions and functional food products.